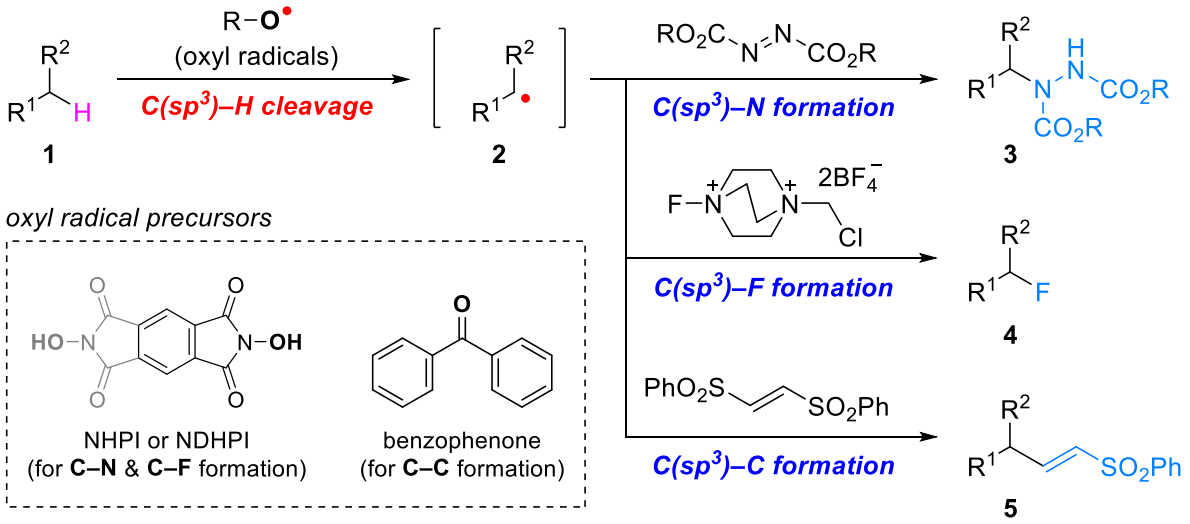
論文の内容の要旨

論文題目：Development of Oxyl Radical Mediated C(sp^3)–H Transformations
（高反応性オキシルラジカルを利用する C(sp^3)–H 結合変換法の開発）

氏名：天岡　佑紀

1. Introduction

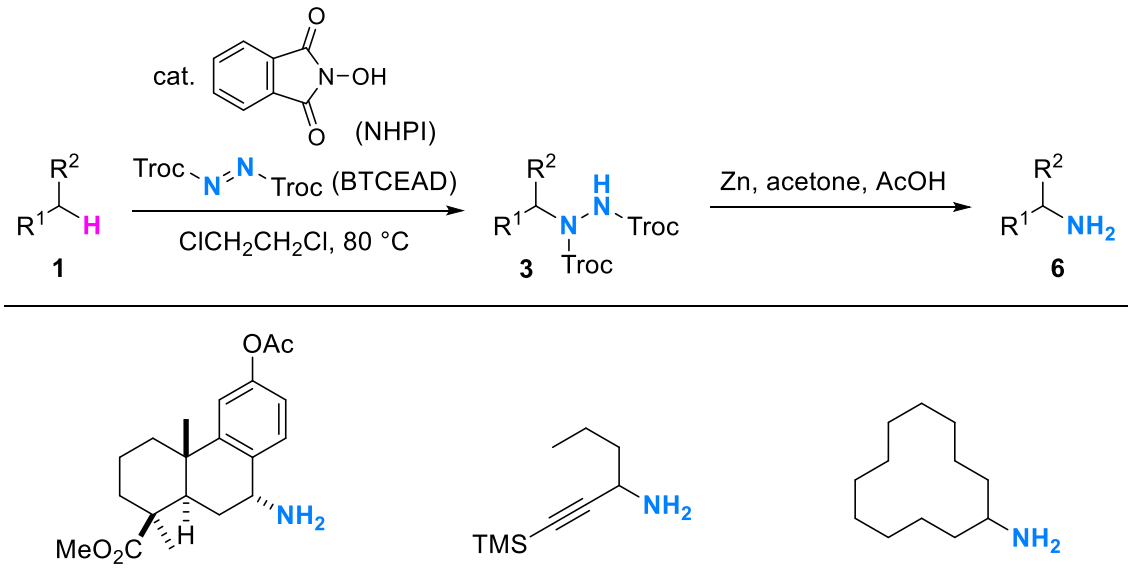
In this thesis, a development of three new methodologies for direct transformation of C(sp^3)–H bonds has been discussed (Scheme 1). The high chemoselectivity was realized by using oxyl radicals, which are the key species having a highly electrophilic and strong hydrogen-abstracting character. Namely, the oxyl radical species abstracted the hydrogen from the most electron-rich and weakest C(sp^3)–H bond of starting material **1**. The generated electron-rich carbon radical intermediate **2** was trapped with various electrophilic radical acceptors to achieve the direct C(sp^3)–H amination (**3**),[1] C(sp^3)–H fluorination (**4**)[2] and C(sp^3)–H alkenylation (**5**).



Scheme 1. Oxyl radical-mediated C(sp^3)–H transformations

2. Development of Oxyl Radical Mediated C(sp^3)–H Amination

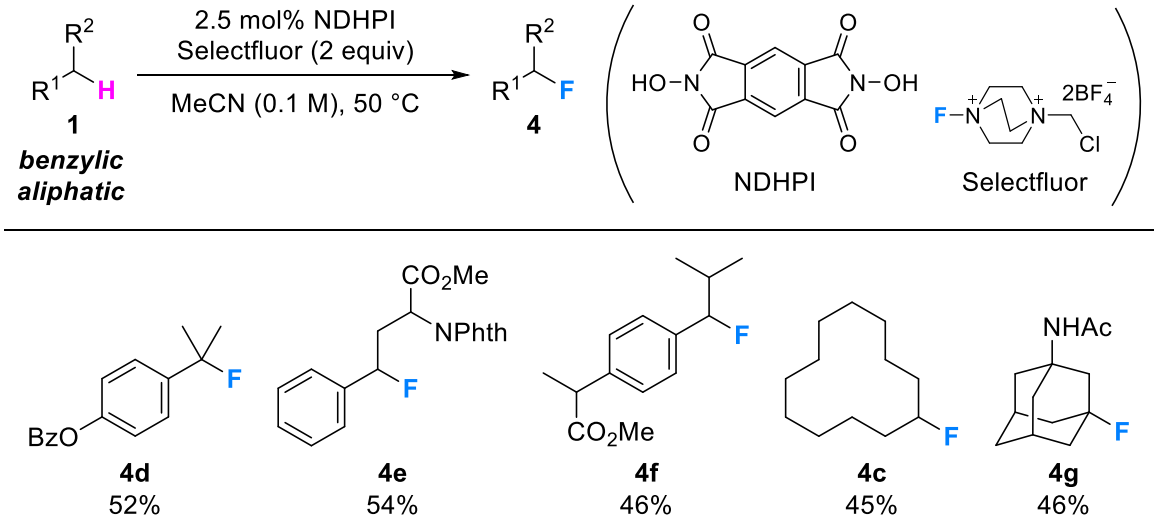
The direct amination of C(sp^3)–H bonds was successfully developed using the combination of *N*-hydroxyphthalimide (NHPI)[3] catalyst and dialkyl azodicarboxylates (Scheme 2). The reaction was found to be applicable to the amination of benzylic, propargylic and even aliphatic C(sp^3)–H bonds (**1**) to provide the corresponding hydrazines **3**. When bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) was employed as a radical acceptor, the generated adducts **3** was able to be readily converted to the corresponding primary amines **6** via zinc-mediated reductive Troc removal and N–N bond cleavage. Since various primary amines such as **6a**, **6b** and **6c** were synthesized only in two steps, the present amination protocol serves as a powerful tool for the efficient synthesis of complex nitrogen-containing natural products and pharmaceuticals.



Scheme 2. Oxyl radical-mediated C(sp^3)–H amination

3. Development of Oxyl Radical Mediated C(sp^3)–H Fluorination

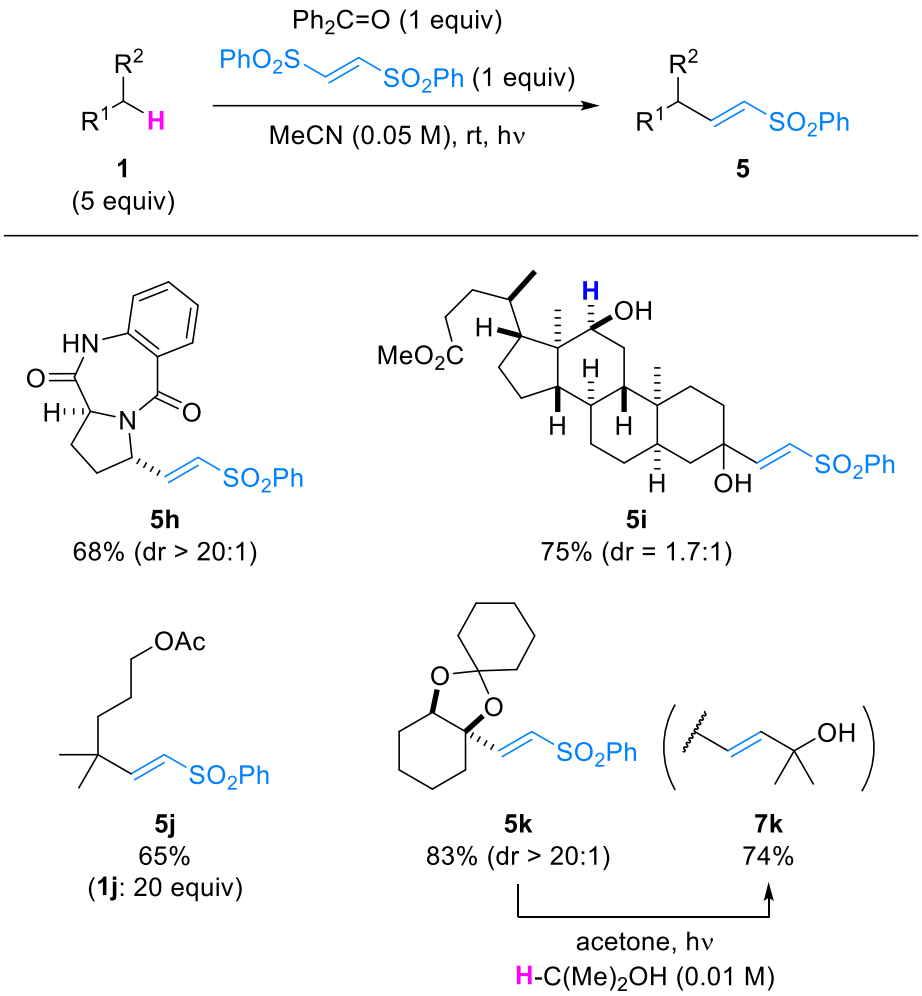
Based on the similar strategy, the direct fluorination of C(sp^3)–H bonds was developed using the combination of *N*,*N*-dihydroxypyromellitimide (NDHPI) catalyst and Selectfluor (Scheme 3). In this reaction, benzylic C(sp^3)–H bonds (**1-d-f**) and aliphatic C(sp^3)–H bonds (**1-c** and **1-g**) were successfully converted to C(sp^3)–F bonds (**4**) only in a single step. The present fluorination method serves as a unique transformation for the rapid synthesis of various fluorinated compounds with pharmaceutical and agrochemical applications.



Scheme 3. Oxyl radical-mediated C(sp^3)–H fluorination

4. Development of Oxyl Radical Mediated C(sp^3)–H Alkenylation

The direct alkenylation of C(sp^3)–H bonds was developed using the combination of benzophenone and 1,2-bis(phenylsulfonyl)ethylene under photoirradiation[4] (Scheme 4). The reaction introduced the sulfonylalkene unit into aminyl (**5h**), alcoholic (**5i**), aliphatic (**5j**) and ethereal C(sp^3)–H bonds (**5k**) in the highly chemoselective and stereoselective manner. Moreover, the derived sulfonylalkene **5k** was readily converted to the corresponding isopropanol adduct **7k** via the consecutive photo-induced radical substitution. From these aspects, the present protocol serves as an efficient method for constructing versatile carbon skeletons of structurally complex compounds.



Scheme 4. Oxyl radical-mediated C(sp^3)–H alkenylation

5. Conclusion

In conclusion, a unified C(sp^3)–H amination, fluorination and alkenylation methodologies have been developed by using oxyl radical species and electrophilic radical acceptors. These reactions are highly reliable because of their predictable chemoselectivity towards the most electron-rich C(sp^3)–H bond in the target molecule. Therefore, the present protocols can not only dramatically simplify synthetic routes to structurally complex molecules, but also make it possible to rapidly synthesize the diversely functionalized compounds from the easily available starting materials.

6. References

(1) Amaoka, Y.; Kamijo, S.; Hoshikawa, T.; Inoue, M. *J. Org. Chem.* **2012**, *77*, 9959. (2) Amaoka, Y.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, *15*, 2160. (3) (a) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393. (b) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800. (4) Fagnori, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev.* **2007**, *107*, 2725.